Initial design and physical characterization of a polymeric device for osmosis-driven delayed burst delivery of vaccines

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Initial Design and Physical Characterization of a Polymeric Device for Osmosis-Driven Delayed Burst Delivery of Vaccines†

Running title: delayed burst release device

Ferry PW Melchels*, Ingo Fehr, Annika S Reitz, Urip Dunker, Kenneth W Beagley, Tim R Dargaville, and Dietmar W Hutmacher*

Dr FPW Melchels, Prof Dr KW Beagley, Dr TR Dargaville, Prof Dr DW Hutmacher
Queensland University of Technology, Institute of Health and Biomedical Innovation, 60 Musk Avenue, Kelvin Grove, 4059 Queensland, Australia
E-mail: dietmar.hutmacher@qut.edu.au
Phone: +61 7 3138 6077

Dr FPW Melchels
University Medical Center Utrecht, Dept. of Orthopaedics. Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
E-mail: f.p.w.melchels@umcutrecht.nl
Phone: +31 6 4034 4054

I Fehr MSc, AS Reitz BSc, U Dunker MSc
RWTH Aachen University, Institut für Textiltechnik & Institut für Angewandte Medizintechnik. Templergraben 55, 52062 Aachen, Germany

Prof Dr DW Hutmacher
Technical University of Munich, Institute for Advanced Study. Lichtenbergstraße 2 a, 85748 Garching, Germany

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Abstract

Achieving the combination of delayed and immediate release of a vaccine from a delivery device without applying external triggers remains elusive in implementing single administration vaccination strategies. Here a means of vaccine delivery is presented, which exploits osmosis to trigger delayed burst release of an active compound. Poly(ε-caprolactone) capsules of 2 mm diameter were prepared by dip-coating, and their burst pressure and release characteristics were evaluated. Burst pressures (in bar) increased with wall thickness (t in mm) following $P_{burst} = 131 \cdot t + 3 \cdot 4$ ($R^2 = 0.93$). Upon immersion in PBS, glucose solution-filled capsules burst after 8.7 ± 2.9 days. Copolymers of hydrophobic ε -caprolactone and hydrophilic polyethylene glycol were synthesized and their physico-chemical properties were assessed. With increasing hydrophilic content, the copolymer capsules showed increased water uptake rates and maximum weight increase, while the burst release was earlier: 5.6 ± 2.0 days and 1.9 ± 0.2 days for 5 and 10 wt% polyethylene glycol, respectively. The presented approach enables the reproducible preparation of capsules with high versatility in materials and properties, while these vaccine delivery vehicles can be prepared separately from, and independently of the active compound.

Introduction

Immunization has played a significant role in the widespread prevention and eradication of disease throughout the world, ever since the development of the smallpox vaccine in the 18th century (Ada et al., 1999). Therefore, it is not surprising that immunization programs have become an integral component of government health care systems throughout the developed and developing world (Amorij et al., 2012; Chen et al., 2011). Immunization involves introducing a pathogen-specific antigen to intentionally elicit an immune response. This primes the body's immune system to respond to the pathogen, to provide protection against future exposure via natural transmission (Ada et al., 1999; Ada and Peter, 1998).

One of the current challenges with immunization technology is that, for many vaccines to achieve complete immune protection, the patient requires a secondary dose of the vaccine at a specific time interval following the original vaccine administration (Ada and Peter, 1998). For example, in many countries, infants receive 8 different vaccines during their first 12 months of life, with up to 5 separate administrations or 'booster shots' for each vaccine. Timely administration of booster shots can be challenging, particularly where access to medical care is limited, such as in remote communities and developing countries, and for the immunization of wildlife (Kollipara et al., 2012) where recapture of each animal can be difficult. In some cases, even with an established and accessible medical system, patients do not receive timely administration of vaccines due to reasons such as migrating populations, inconvenience, discomfort, lack of education about the importance of the repetitive administration or misconceptions on perceived dangers of vaccination.

The development of single-administration vaccines (SAV) has been a growing area of interest within the immunology and biomaterials science fields for several decades. SAVs are of particular interest for two main reasons: 1) to eliminate the need for booster shots, significantly reducing logistical costs associated with repeat administrations and 2) to ensure the optimal time-delay between primary and secondary exposure to the antigen, resulting in maximum immunity against the pathogen. Approaches to release of antigens in a controlled manner are mostly based on liposomes, unilamellar

vesicles, emulsions, degradable polymeric microparticles or self-exploding micro capsules (De Geest et al., 2009; Zhao and Leong, 1996). The use of biodegradable microparticles administered by subcutaneous injection is perhaps the most commonly reported strategy (Cleland, 1999). There are several variations to the technology, with regards to the polymer matrix formulation including polylactide, polylactide-glycolide, polyethylene glycol, collagen, poly(ε-caprolactone), copolymers and blends, but essentially all of these involve the encapsulation of the antigen in a biodegradable polymer matrix. The release kinetics from biodegradable microparticles is usually triphasic: initial release of antigen from the surface of the microparticle followed by a lag period and then a continuous diffusion release phase. In most cases, the continuous diffusive release phase is in the order of weeks. This is not a desirable release profile as it does not mimic the instantaneous, concentrated antigen dose experienced with traditional needle injections, which could lead to induced tolerance (Cleland, 1999) as well as potentially hindering clinical approval. Furthermore, the quantity of antigen released at the maximal release load, is significantly less than total antigen quantity that is introduced in the production process. This implies that higher quantities of active compound are required during production of the microparticles, resulting in higher production costs. Numerous approaches have been used to prepare microcapsules with burst release characteristics designed to release a drug payload under certain conditions. Stimuli include high temperature (Volz et al., 2007), reducing reagents (Zhang et al., 2011), light (Bédard et al., 2010) and slightly acidic conditions (Zhang et al., 2012). Although elegant, none of these methods utilize suitable triggers for subcutaneous *in vivo* release. A more applicable approach exploited by De Geest *et al.* is to use osmotic pressure as the triggering mechanism to cause physical rupture of a vaccine-containing capsule (De Geest et al., 2008; De Geest et al., 2009) (De Geest ref needed Journal of Controlled Release 135 (2009) 268–273, Adv. Mater. 2008, 20, 3687–3691). While there have been various osmotically controlled drug delivery technologies reported in literature, these systems generally endeavor to achieve zero-order release kinetics, *i.e.* continuous release and, as previously mentioned, this is not the desired release kinetics for vaccine delivery.

De Geest *et al.* achieved instantaneous delayed release using polyelectrolyte capsules filled with dextran-methacrylate hydrogel, which degrades via hydrolysis at a rate influenced by the crosslinking density. The concept of polyelectrolyte microcapsules in vaccine technology had previously been used to improve the delivery efficiency of DNA plasmids to the cytoplasm by reducing nuclease attack, thereby enhancing the antibody response, but not as a delay mechanism (Selina et al., 2009; Singh et al., 2000). By using a similar polyelectrolyte shell but introducing a dextran core, De Geest *et al.* were able to regulate the osmotic pressure, such that over time the degradation of the dextran causes a gradual increase in osmolarity resulting in higher internal hydrostatic pressure, until the capsules rupture and release their contents. A number of limitations remain with the self-exploding microcapsule technology, being variations in the size of microparticles leading to a spread in the burst times, potential redistribution of microcapsules throughout, or clearance from the body, as well as the impossibility to remove the particles in case of adverse events.

Here we demonstrate a novel delivery platform to overcome most of the restrictions of current multiphasic vaccine delivery systems. We hypothesize that polymer tubes containing a model dye together with glucose as an osmotically active agent (osmogent) will allow slow influx of water at a controlled rate, ultimately resulting in bursting of the membrane as the hydrostatic pressure overcomes the burst pressure of the capsule, thus instantaneously releasing the payload (Figure 1). Osmotically activated capsules were prepared from a series of PCL and PCL-PEG copolymers with varying water permeability. The polymers and capsules were characterized, and the proof of concept of delayed burst delivery was demonstrated.

Materials and Methods

Polymers: Poly(ε-caprolactone) (PCL) was used as received (Perstorp, CAPA 6500). Linear polyethylene glycol (PEG, Fluka (8 and 20 kg mol^{-1}) and Sigma Aldrich (35 kg mol^{-1})) was first dried by azeotropic distillation with toluene using Dean Stark apparatus, and then employed as macro-initiator for the preparation of PCL-PEG-PCL triblock copolymers by ring opening

polymerization of ε-caprolactone (Sigma Aldrich), for 2 days at 130 °C in the presence of $Sn(Oct)_2$ (Sigma Aldrich) as a catalyst, under an argon atmosphere. The polymers were then dissolved in chloroform and precipitated from ethanol (10 % and 20 % PEG) or diethyl ether (30 % PEG), filtered and air-dried followed by vacuum drying. Targeted molecular weights of the co-polymers were between 66 and 100 kg mol^{-1}. For simplicity, the nomenclature for the copolymers is *x*PEG, in which *x* is the intended weight percentage of PEG (making 100-x the intended weight percentage of PCL).

Proton nuclear magnetic resonance spectroscopy (^{1}H-NMR, Bruker Avance 400 MHz) was used to confirm PEG/PCL molar ratio and purity of the products. Differential scanning calorimetry was performed using a DSC-Q100 (TA Instruments) at a rate of 10 °C min^{-1} to determine melting and crystallization characteristics. The purified polymers were processed into 1 mm thick sheets by compression molding (140 °C, 14 MPa) using a custom made heated press, prior to cutting dumbbell shaped specimen for tensile testing (Instron MicroTester equipped with 500 N load cell) at a strain rate of 30 % min^{-1}.

Tubes: Tubes were fabricated by dip-coating. Steel rods (10-20 cm length, 2.0 mm diameter) were dipped into a 10% w/v polymer solution in $CHCl_3$ and then rotated at 2 rpm at an angle of 45° for 2 min. The process was repeated twice. Tubes were annealed on the mandrel under partial vacuum (7 mbar) in a glass tube immersed in water at 70°C for 15 min. The tube was decapped and immersed in ethanol for 1 h prior to removal from the rod. The middle section of the tube was used to ensure homogenous wall thickness.

Burst pressure tests were performed at room temperature (Instron MicroTester equipped with 500 N load cell) at 5 mm min^{-1}, corresponding to 83 μL min^{-1}. Tubes were end-capped on one side, filled with water and mounted onto a 14 G needle (2.1 mm outer ∅) attached to a 1 mL glass syringe (Figure 4A) mounted in a custom-made, rig assembled from laser cut polymethyl methacrylate parts. The joint between tube and needle was fixed and made leak-free with a 4 mm shaft clamp and two

O-rings (1.8 mm ∅). Recorded forces were corrected for friction force from the plunger (measured with non-capped tube filled with water) and divided by the surface area of the plunger (16.6 mm^2) to yield pressure values, while the injected volume was calculated as the displacement multiplied by ditto number. The compliance of the setup was found to be negligible.

Osmosis-driven delayed burst release: Tubes (30 mm long, inner diameter 2.0 mm, wall thickness 0.2 mm) made out of PCL, 5PEG and 10PEG were end-capped on one side, filled with saturated glucose supplemented with blue food dye with a syringe, and end-capped air-free on the other side. Specimen (n=3x9) were weighed, immersed in PBS at 37 °C and their weights recorded at intervals. Four out of 27 tubes leaked directly from immersion and were disregarded. The first moment of decreased weight (always corresponding with discoloration of the immersion medium) was taken as the burst moment.

Results

1. Polymer properties

PCL-PEG-PCL triblock copolymers were successfully synthesized with PEG contents close to the intended values (Table I**).** As PCL and PEG homopolymers have comparable melting temperatures, the resulting copolymers melt within the same tight range of 54-56 °C. The melting enthalpy was slightly higher for the PEG-containing polymers than for PCL homopolymer. Crystallization occurred just above room temperature (25-31 °C) at the applied cooling rate of 10 °C min^{-1}.

As intended, the equilibrium water uptake in PBS (osmotic pressure 7.7 bar (Silbernagl and Despopoulos, 2008)) increases significantly as the fraction of the hydrophilic PEG component is increased. The equilibrium water uptake in saturated glucose (909 g L^{-1}, osmotic pressure 165 bar) is considerably lower for all polymers. The difference in water concentration, which is the driving force for the inflow of water into a glucose solution-filled polymer capsule in an aqueous environment, increases sharply with PEG content.

The stiffness of all polymers is comparable in the dry state, namely 250-350 MPa (Figure 2A). More importantly, with increasing PEG content, thus increasing uptake of plasticizing water, the stiffness is reduced by 8 % for PCL up to 65 % for 30PEG. The tensile strength is not considerably affected by the uptake of water, but does decrease with increasing PEG content (Figure 2B). This is an important parameter determining the lag time for delayed burst delivery. Upon prolonged immersion in PBS at 37 °C, the ultimate strength slightly decreases as an effect of polymer degradation by hydrolysis. Not unexpectedly, the rate of degradation is faster for the more hydrophilic polymers, but in no case is the loss in tensile strength significant within the timeframe in which is vaccine delivery is intended (Figure 2C).

2. Capsule characteristics

Tubular parts were fabricated by solution dip coating onto a metal mandrel followed by thermal annealing to remove irregularities and obtain a solid, homogeneous tube wall (Figure 3A). Dip coating was successfully performed with all polymers, however was more facile for lower PEG content. Solvent evaporation led to a rough porous surface (Figure 3B) with increased roughness for higher PEG content, however this was evened out by thermal annealing (Figure 3C). Tubes typically had an internal diameter of 2 mm (corresponding to the diameter of the mandrel) and wall thickness between 0.1 and 0.4 mm. Wall thickness could easily be varied by changing the number of dips for dip coating. The wall thickness was homogenous throughout the tube (Figure 3A); a typical wall thickness distribution (Figure 3D) shows a standard deviation of 0.021 mm at an average of 0.171 mm.

Tubular capsules were filled with liquid using a micropipette, followed by sealing. Sealing was performed by inserting a cylindrical PCL plug into the distal part of the tube, followed by melt-sealing of the tube wall onto the plug. For a reproducible sealing process, a sealing device was developed (Figure 3E). It comprises one copper block which contains the tube with plug and is used at room temperature (blue in the CAD drawing), and a copper block that is assembled onto the first block with guiding rigs after pre-heating (red in the CAD drawing), effectively melt-sealing the plug into the tube. Quick solidification follows as the smaller hot block conducts its heat to the larger cold block, which acts as a heat sink.

The burst pressures of produced tubes were tested using a custom-made device that allows controlled inflation of the tube with liquid from a syringe, using a mechanical testing setup (Figure 4A). Testing of tubes of comparable geometry but from different polymers showed a minor decrease in burst pressure when PEG content was increased from 0 to 5 to 10 %, but a sharp decline when further increasing PEG content to 20 and 30 % (Figure 4B, C). These trends are consistent with the changes in measured uniaxial tensile strengths (Figure 2B). The burst pressures of PCL tubes of

varying wall thickness were systematically lower than predicted using equations S1 and S2 (Supplementary Info) with the measured tensile strength as input parameter. However, the values were highly reproducible, with linear dependence on wall thickness t: $P_{burst} = 131 \cdot t + 3.4$ with $R^2 = 0.93$ (Figure 4D).

3. Osmosis-driven delayed burst release experiment

Tubes filled with osmogent and dye (as a model compound) steadily increased in mass due to water uptake when immersed in PBS, and showed delayed burst release behavior as confirmed by the release of dye (Figure 5). With increasing PEG content in the capsule polymer, the water uptake was higher and more rapid, and the dye was released earlier. PCL tubes burst within 8.7 ± 2.9 days, 5PEG tubes in 5.6 ± 2.0 days and 10PEG tubes in 1.9 ± 0.2 days. The 20PEG and 30PEG materials were not included because of their poor mechanical robustness and high water uptake.

Discussion

Complete immune protection upon a single administration is the holy grail of vaccine delivery research. In this research endeavor, two main approaches can be distinguished: the use of alternative immunogenic compounds, or the controlled release of antigen using a biomaterials approach. The first approach, which includes the use of defined subunit antigens, viruses (live or attenuated) or vectors (viral or DNA) encoding part of the pathogen genome, is not without risks (while subunit vaccines may require strong adjuvants to elicit protective immunity). The research into biomaterials-based controlled release of antigens is mainly divided into the use of microparticles or self-exploding (osmotic) microcapsules, extended by the monolithic osmotic capsules introduced here. These osmotic capsules present a versatile delivery platform, in which the lag time for burst release may be tailored through the choice of polymer, mechanical properties, degradation profile, capsule wall thickness/geometry and concentration of the osmogent.

In this study, osmosis-driven delayed burst delivery from monolithic implantable capsules was demonstrated, including experimental data studying the influence of polymer hydrophilicity on burst

time. The choice of PCL and PCL-PEG-PCL as the capsule materials was based on their widely-accepted use as implantable materials (characterized by mild implantation biology and minor fibrous tissue encapsulation (Woodruff and Hutmacher, 2010)), ease of processing and the ability to vary the hydrophilic/hydrophobic balance depending on PEG content. After the intended release of vaccine, PCL is fully degraded after 2-3 years in the subcutaneous environment, largely independent of implant geometry (Sun et al., 2006); PEG-containing copolymers can be expected to degrade faster due to higher water uptake hence faster hydrolytic degradation (Figure 2C). The water uptake of glucose-filled PCL and copolymer capsules was faster than intuitively expected based on the hydrophobic nature of PCL (water uptake of 0.5%, Table I). Therefore, a 5% PEG copolymer was synthesized and added to the range for the osmosis-driven burst release experiment. Based on the observed lag times for burst delivery compared to the desired intervals between prime and booster shots, PCL homopolymer will be the most suitable candidate of this set of materials for the intended purpose. The suitability of wall thickness as a control parameter was demonstrated by showing the highly predictable increase in burst pressure with thickness (Figure 4D). The effect of these and other design parameters (PEG content, osmogent concentration, internal diameter) can be evaluated quantitatively using a simple model similar to the one developed by Kuethe *et al.* (Kuethe et al., 1992). In our version, in particular the decline in water inflow due to dilution of the osmogent has been considered (Supplementary Info). In order to extend the burst lag time of PCL capsules from the current 8.7 days up to a more relevant time for booster shots (e.g. 35 days – a factor 4 times higher), one could, for example, increase both geometrical parameters (diameter and wall thickness) by a factor 2. Alternatively, one could use internal diameter 3 mm with 0.4 mm wall thickness and a glucose solution of 425 g/L. Further decreasing the osmogent concentration is unwise, as this leads to a situation where at the calculated burst time osmotic and hydrostatic pressure are almost in equilibrium, which means an unpredictable delay time that is highly sensitive to small changes in properties or environmental conditions. To obtain longer delay times without increasing the capsule size, polymers with lower water permeability are required. Here we use the model to assess the

influence of design parameters; calculation of absolute burst times requires all constituent parameters to be known, including the permeability of the polymer to water, and time-dependent mechanical behavior (e.g. creep).

The use of monolithic osmotic capsules has many specific advantages over previously described approaches. Firstly, it is highly versatile as a wide range of polymers can be used and prepared into capsules with a range of delivery times from hours to potentially months. The fabrication process is simple, in this case dip coating was used, although for mass production for actual future use we envision the application of industrial melt extrusion techniques to produce polymer tubing with high accuracy and very low cost. Another advantage is that the choice of payload is independent from the capsule material or method of preparation. As the reservoir device is first prepared and then filled with osmogent and vaccine, the vaccine will not be exposed to any processing (e.g. heat or organic solvents). On the contrary, while PLGA microspheres have proven successful for the timely delivery of several antigens, this technology has not been applied to viruses or bacteria that make up a large part of existing vaccines (Cleland, 1999). The inevitable use of harsh organic solvents may destroy the active compounds. Furthermore, the payload will be incorporated quantitatively in the osmotic capsules. For microparticles or self-exploding microcapsules, loading efficiencies are often low and precise quantities and concentrations of the antigen contained within the formulations unknown. In addition, existing vaccine formulations have the potential to be used with these osmotic capsules without substantial modification, provided the antigen remains stable inside the capsule up until its release and can be concentrated into the necessary volume (approximately 70 μL for the capsule size studied here). Ordinarily vaccine formulations are prepared as dilute solutions, however, capsule delivery would require concentration of the vaccine to enable the dosing required. Therefore, consideration of possible precipitation and inactivation should be given specific to the antigen used. Once implanted, the monolith will prevent redistribution throughout, or clearance of the active compounds from the body between the time of administration and the release. The other important

advantage of the use of a single, monolithic device is that it ensures a single pulse of active compound.

For this type of vaccination device to be translated to use in animals or humans, cost is a major consideration. Polymer tubing can be easily manufactured at low cost by extrusion methods. Sterilization, filling and capping can be done in an automated way and there are no costs for solvents or laborious processes. Typically, the material cost for a single delivery device (excluding vaccine) in the order of a few tens of cents (for 70 mg of a biodegradable polymer and 150 mg glucose). In summary, monolithic osmosis-driven delayed burst release capsules have many advantages when compared to microparticles and self-exploding microcapsules (Table II). The major disadvantage is the method of administration; the capsule needs to be implanted under the skin using a large diameter needle, as opposed to an intramuscular or intravenous injection. However, a device with similar geometry and stiffness (Implanon™ contraceptive) is being used successfully on a large scale in women whereby the application is performed by nurses and general practitioners without the need for specific training. Thus, existing methods of device implantation (Implanon™ applicator, a 14G needle with built-in plunger) can be employed with relative ease. One potential disadvantage is the possibility of local hypertonicity within the interstitial fluid immediately after capsule burst due to the osmogent release. Some cell necrosis would be likely under these circumstances but would only be transient until isotonic conditions are re-established. To study the effects of osmogent-induced hypertonicity *in vivo* models would be required.

To develop systems that release vaccines in a controlled manner following single administration, it should be considered that the current regimen of delivering single pulses at predetermined intervals may not be ideal. The current approach of repeated bolus injections has proven to work, but it may be the gold standard for its practicality rather than inducing the strongest, most long-lived immunologic response. Indeed, some studies suggest that rather than repeated bolus injections, exponentially increasing doses of antigen (mimicking pathogen replication) may illicit the strongest immune response (Johansen et al., 2008). Alternative approaches deliver decreasing vaccine doses in

order to expand the highest affinity B and T cell responses. Yet another study showed that an initial pulse of antigen followed by a trickle delivery works equally well as pulsatile delivery (Spiers et al., 2000). The optimum dosing schedule will vary for different antigens and will have to be established using tools such as osmotic pumps (Cleland et al., 1996). Nevertheless, there is consensus on the fact that pulsatile release of any form will outperform a continuous release approach, as the latter potentially evoke a low-dose tolerance, where antibody titers are low and do not neutralize (Cleland et al., 1996; Spiers et al., 2000). The approach introduced here allows for multiple pulses by using multiple capsules, or one capsule containing multiple chambers that can each rupture and release at distinct time points.

A major requirement for this and many other vaccine delivery systems to work is for the vaccine to remain active upon long-term storage in the body, including a relatively high temperature and hydrated condition. As proteins, antigens are prone to denaturation, and live organisms or viruses may be even more sensitive. Thorough stability tests will thus have to be performed before any attempt of immunization with this delivery platform can be done. Possibly, active compounds can be further protected, *e.g.* by encapsulation in microparticles that will remain stable inside the capsule, but are degraded swiftly upon contact with body fluid after delayed burst delivery.

Osmosis has been exploited for time-controlled release of active compounds in many forms, most commonly utilized to achieve *sustained* release. To that end, capsules filled with an active compound and an osmogent have a small orifice through which the drug is expelled in a sustained manner by swelling of the osmogent (Verma et al., 2002). The commercially available OROS™ system based on this technology has been employed for oral delivery of drugs in many therapeutic areas including cardiovascular medicine, endocrinology, urology, and central nervous system therapeutics (Conley et al., 2006). The release properties of such osmotic devices are to a large extent independent of physiological factors such as pH and the presence of enzymes, resulting in a high *in vitro* to *in vivo* correlation. In the absence of an orifice, the osmotic effect induces a gradual increase of the hydrostatic pressure inside the semi-permeable membrane. This pressure increase can

be used to achieve instantaneous release after a lag period, when the burst pressure of the membrane is overcome.

Drug release devices have also been reported where ejection of a plug, expansion of an orifice or rupturing of a membrane was triggered by an increased hydrostatic pressure after osmosis-driven water uptake (Barzegar-Jalali et al., 2006; Schultz et al., 1997). Application to vaccine booster shots has been suggested (Gresser et al., 1995) and appropriate delay times have been shown for injectable systems such as the self-exploding osmotic microcapsules described above (De Geest et al., 2009; Stubbe et al., 2004). Monolithic devices however have typically been targeted at the gastrointestinal tract, and to our knowledge any reported delay time of such systems is within 48 h (Reddy et al., 2009; Vipul and Moinuddin, 2012). In this study we prepared capsules that release their payload by burst delivery after 8.7 ± 2.9 days, and suggested means of further extending the lag time based on a sophisticated version of existing models of delayed burst release. Analogously to the orifice-based osmotic systems, the behavior of the osmosis-driven delayed burst-release devices can be expected to be mostly independent of external factors, thus presenting a reliable platform for vaccine delivery.

Conclusions

In this work we presented a platform for vaccine delivery, exploiting osmosis to trigger delayed burst release of an active compound. The delivery vehicle is a polymer capsule that can be prepared separately from, and independently of the active compound. The lag time for burst delivery can be tailored through parameters relating to capsule material, capsule geometry and osmogent concentration. Upon immersion in PBS, glucose solution-filled capsules (of the same geometry) prepared from PCL-PEG copolymers with 0, 5 and 10 wt% PEG burst after 8.7 ± 2.9 days, 5.6 ± 2.0 days and 1.9 ± 0.2 days respectively. Furthermore, for PCL tubes with 2 mm internal diameter, the burst pressure increased with wall thickness (t) following $P_{burst} = 0.131 \cdot t + 3.4$, which was reproducible ($R^2 = 0.93$) but systematically lower than predicted. A set of equations was postulated that allows to calculate hydrostatic pressure, volume increase and mechanical load of the capsule when one of the three is given, as well as to obtain a quantitative indication of burst delay time.

Supplementary Information

Supplementary Information is available on the equations governing osmosis-driven delayed burst delivery.

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Table I. Physicochemical properties of (co)polymers

Name	PEG MW [kg mol^{-1}]	PEG in feed [wt%]	PEG NMR [wt%]	T_{melt} [°C]	T_{cryst} [°C]	ΔH_{melt} [J g^{-1}]	water uptake in PBS [wt%]	water uptake in saturated glucose [wt%]	Δwater uptake [wt%]
PCL	-	0	0	54.8	25.2	58	0.5	0.1	0.4
5PEG	6	5	4.8	55.6	30.1	61	3.2	2.9	0.3
10PEG	8	10	14	55.8	29.0	67	7.4	3.7	3.7
20PEG	20	20	19	54.9	30.6	65	19.1	11.9	7.2
30PEG	20	30	28	55.0	30.8	66	35.1	22.1	13.0

Table II. Comparison of advantages and disadvantages of monolithic osmosis-driven delayed burst release capsules compared to microparticles and self-exploding microcapsules for vaccine delivery

	microparticles	self-exploding microcapsules	monolithic osmotic capsules
tailoring delay time	+	-	++
exposure of antigen to harsh conditions	-	+	+
pulse-like delivery	-	+	++
dependence on physiological factors	-	-	+
sterilization	-	-	+
ease of administration	+	+	-
removal if adverse reaction	-	-	+
cost	-	-	++

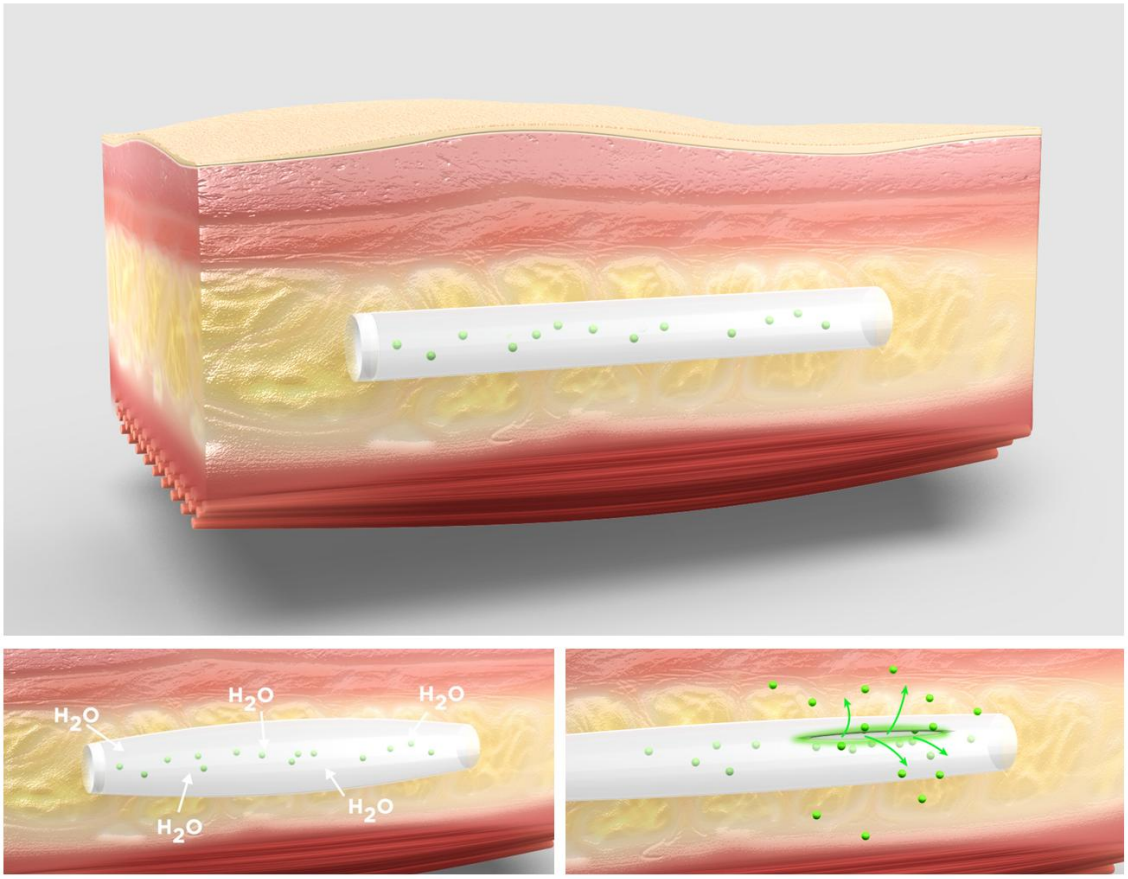

Figure 1. Top: schematic of a polymeric delivery device implanted under the skin. Bottom left: osmosis-driven water uptake swells the capsule. Bottom right: the hydrostatic pressure overcomes the burst pressure; the capsule breaks and releases the vaccine instantly.

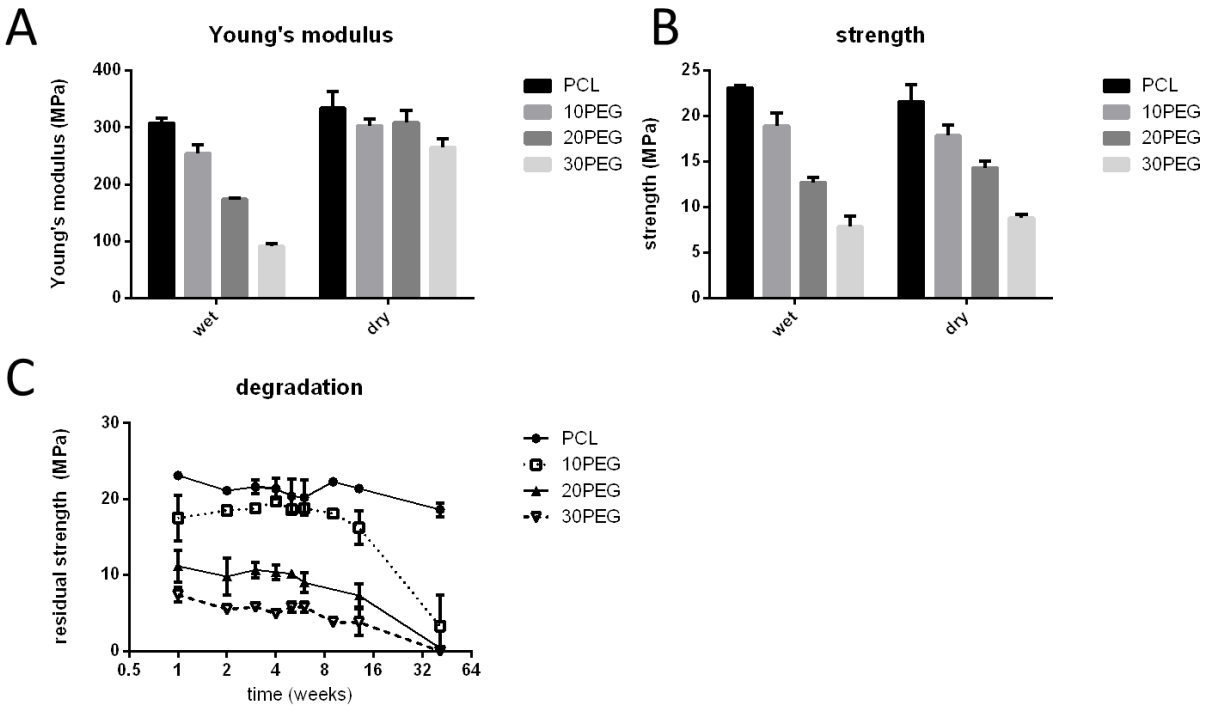

Figure 2. Tensile properties of PCL-PEG-PCL copolymers and PCL homopolymer. Young's modulus (A) and strength (B) in dry state or at equilibrium swelling in PBS. C: loss in strength upon degradation in PBS at 37 °C.

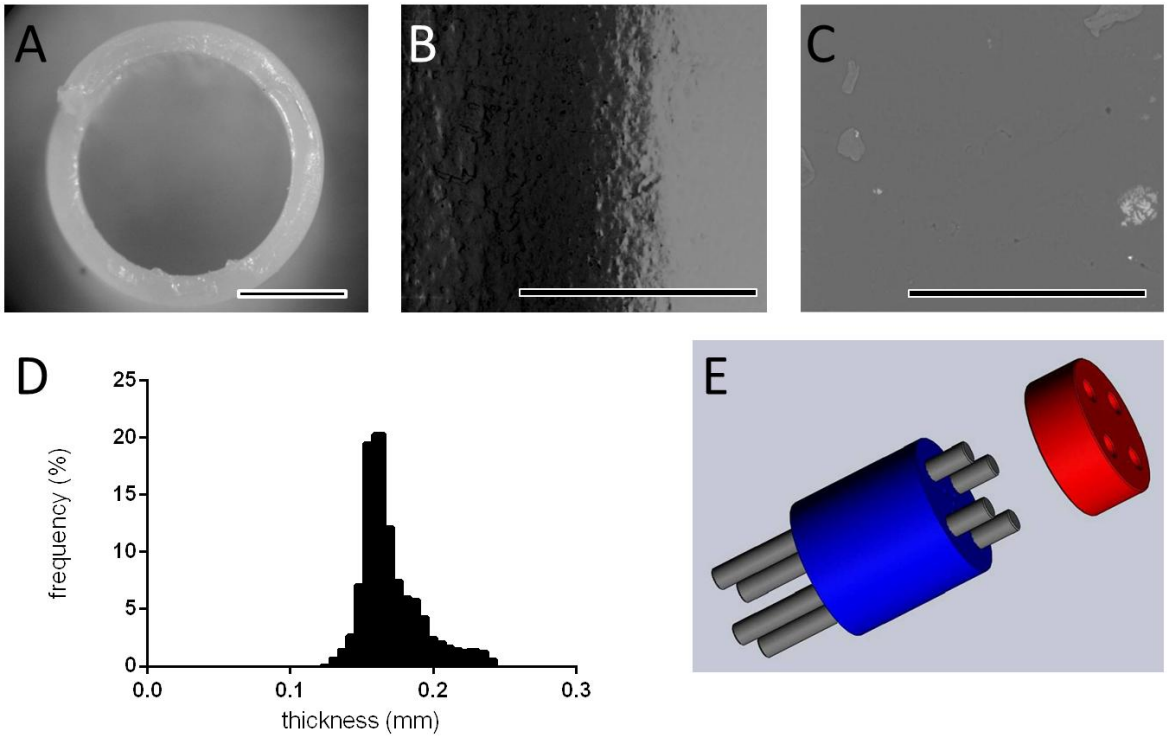

Figure 3. Capsule fabrication. A: photograph of cross section of typical PCL tube (wall thickness 0.30 mm). B: SEM of dip-coated PCL tube showing irregular surface C: PCL tube showing smooth surface after annealing. D: wall thickness distribution of PCL tube. E: CAD design of sealing device. Scale bars are 1 mm (A) and 0.2 mm (B, C).

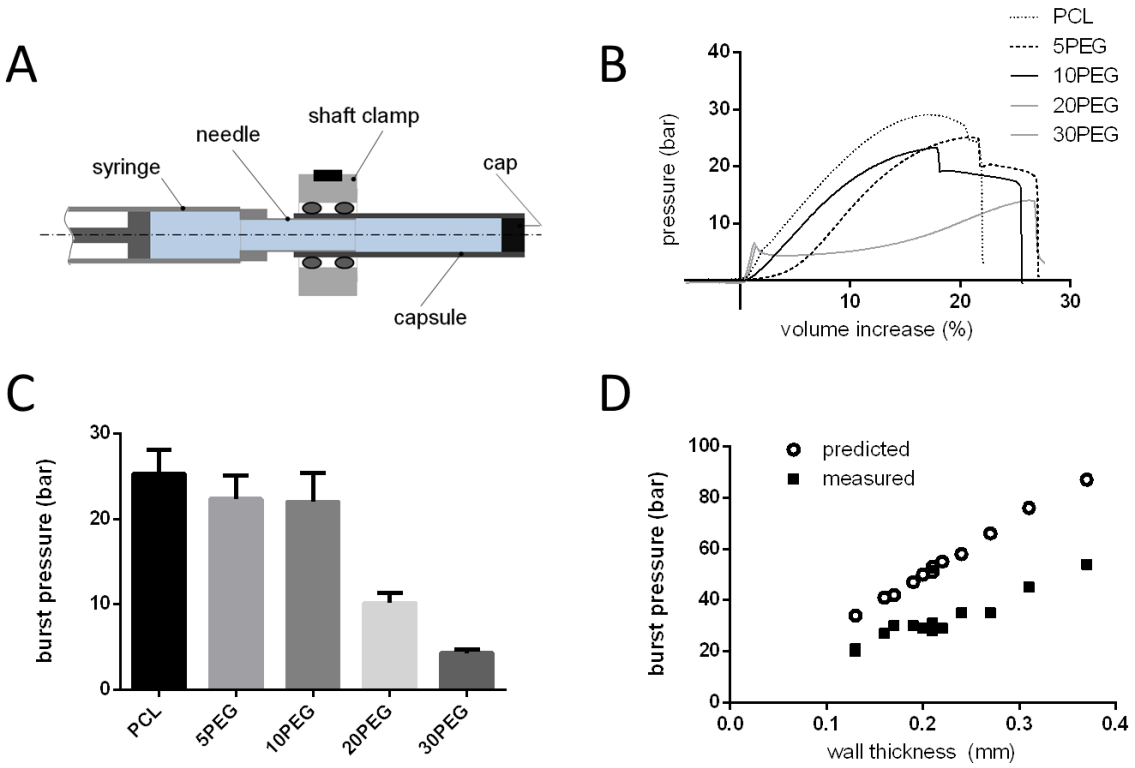

Figure 4. Burst pressure testing. A: schematic of the burst pressure testing setup. B: typical pressure-volume curves for all polymers (0.20 mm wall thickness). C: burst pressure for different polymer compositions (0.20 mm wall thickness). D: burst pressures of PCL capsules of varying wall thicknesses.

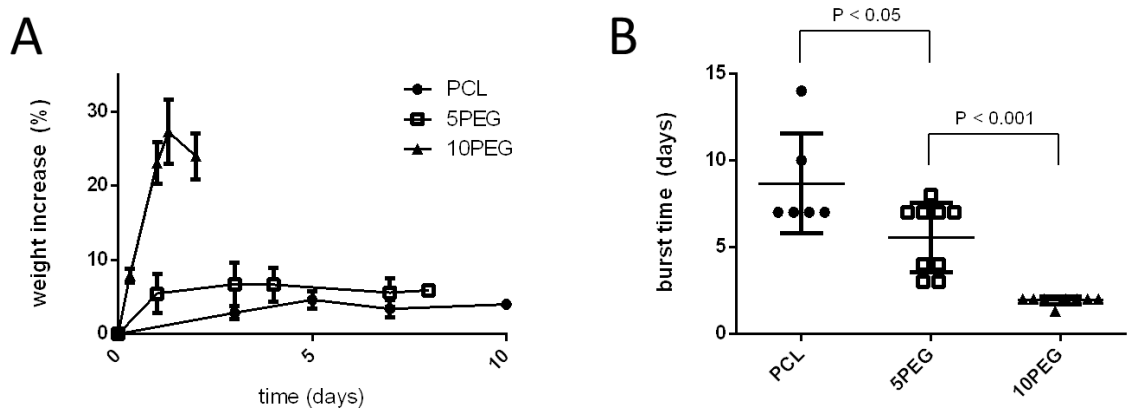

Figure 5. Osmosis-driven delayed burst release. A: relative weight increase of tubes filled with saturated glucose and dye for different polymer compositions upon immersion in PBS. B: delay times for release: mean, standard deviation and p-values (unpaired t-test, N=6-9).

